

**PALM INTRANET**

KIN

Day : Tuesday
 Date: 7/13/2004
 Time: 15:10:38

Inventor Information for 10/800918

Inventor Name	City	State/Country
SINGER, CLAUDE	KFAR SABA	ISRAEL
LIBERMAN, ANITA	TEL AVIV	ISRAEL
FINKELSTEIN, NINA	HERZLIYA	ISRAEL

[Appn Info](#) [Contents](#) [Petition Info](#) [Atty/Agent Info](#) [Continuity Data](#) [Foreign Data](#)

Search Another: Application# or Patent# PCT / / or PG PUBS # Attorney Docket # Bar Code #

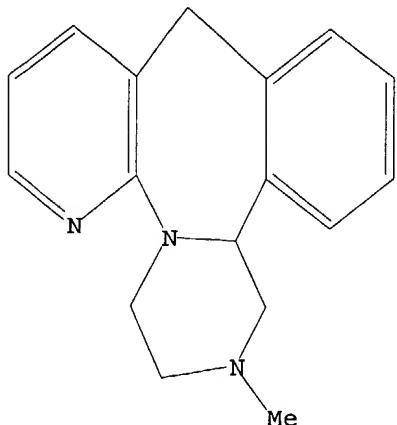
To go back use Back button on your browser toolbar.

Back to [PALM](#) | [ASSIGNMENT](#) | [OASIS](#) | Home page

L Number	Hits	Search Text	DB	Time stamp
1	183	540/578	USPAT	2004/07/13 15:09
2	268187	crystall\$	USPAT	2004/07/13 15:09
4	118	540/578 and crystall\$	USPAT	2004/07/13 15:09
3	85	mirtazapine\$	USPAT	2004/07/13 15:09
5	5	mirtazapine\$ and (540/578 and crystall\$)	USPAT	2004/07/13 15:09

L1 STRUCTURE UPLOADED

=> d 11
 L1 HAS NO ANSWERS
 L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 11
 SAMPLE SEARCH INITIATED 15:15:11 FILE 'REGISTRY'
 SAMPLE SCREEN SEARCH COMPLETED - 12 TO ITERATE
 100.0% PROCESSED 12 ITERATIONS
 SEARCH TIME: 00.00.01
 3 ANSWERS
 FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 33 TO 447
 PROJECTED ANSWERS: 3 TO 163

L2 3 SEA SSS SAM L1

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 FULL SCREEN SEARCH COMPLETED - 223 TO ITERATE

100.0% PROCESSED 223 ITERATIONS
 SEARCH TIME: 00.00.01
 53 ANSWERS

L3 53 SEA SSS FUL L1

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 COST IN U.S. DOLLARS SINCE FILE TOTAL
 ENTRY SESSION
 FULL ESTIMATED COST 148.15 148.36

FILE 'CAPLUS' ENTERED AT 15:15:23 ON 15 SEP 2003
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FILE COVERS 1907 - 15 Sep 2003 VOL 139 ISS 12
FILE LAST UPDATED: 14 Sep 2003 (20030914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L4 311 L3

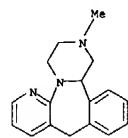
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L5 9 L4 AND CRYSTALL?

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LS ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2003:570816 CAPLUS
 DOCUMENT NUMBER: 138:13873
 TITLE: Sedative non-benzodiazepine formulations
 INVENTOR(S): O'Toole, Edel; Fogarty, Siobhan
 PATENT ASSIGNEE(S): Bioval Laboratories Inc., Barbados
 SOURCE: PCT Int. Appl., 59 pp.
 CODEN: PIKXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE
 WO 2003059349 A1 20030724 WO 2003 1E1 20030109
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
 CN, CO, CR, CU, CZ, DE, DE, DK, DK, DZ, EC, EE, ES,
 FI, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
 KE, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
 MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK,
 SL, TJ, TM, TN, TR, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
 ZW, AM, AZ, BY
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
 NL, PT, SE, SI, SK, TR, BF, BJ, CG, CI, CM, GA, GN, GQ, GW,
 ML, MR, NE, SN, TD, TG
 US 2003165566 A1 20030904 US 2003-338876 20030109
 PRIORITY APPLN. INFO.: US 2002-346613P P 20020110
 AB The invention provides for an enhanced absorption pharmaceutical
 composition comprising a plurality of microparticles, each microparticle comprising
 at least one sedative non-benzodiazepine, at least one spherulisation aid,
 and at least one solubility enhancer. The microparticles of the
 invention are further incorporated into an oral fast-dispersing dosage form. For
 example, microparticles were prepared containing zolpidem tartrate 15%,
 Gelucire 50/13 35%, and distilled monoglyceride (Myraplex) 50%. Microparticles
 obtained were then coated for taste masking with a coating solution
 containing a 60:30:10 ratio of Eudragit NE30D, talc, and Methocel. The coated
 microparticles were used for preparation of tablets.
 IT 85650-52-8, Mirtazapine
 RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological
 study); USES (Uses)
 (preparation of microparticles for enhanced oral bioavailability of
 non benzodiazepine sedatives)
 RN 85650-52-8 CAPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b hexahydro-2-
 methyl- (9CI) (CA INDEX NAME)

LS ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



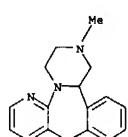
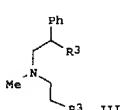
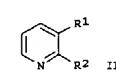
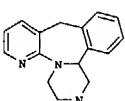
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
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FORMAT

LS ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
 ACCESSION NUMBER: 2003:282146 CAPLUS
 DOCUMENT NUMBER: 138:304301
 TITLE: Novel synthesis and crystallization of
 piperazine ring-containing compounds such as
 mirtazapine
 INVENTOR(S): Singer, Claude; Liberman, Anita; Finkelstein, Nina
 PATENT ASSIGNEE(S): Israel
 SOURCE: U.S. Pat. Appl. Publ., 9 pp., Cont. in-part of U.S.
 Ser. No. 552,485.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

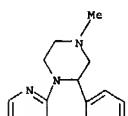
PATENT NO. KIND DATE APPLICATION NO. DATE
 US 2003069417 A1 20030410 US 2002-206344 20020729
 US 2001051718 A1 20011213 US 2001-900646 20010706
 US 6545149 B2 20030408
 US 2003088094 A1 20030508 US 2002-283093 20021030
 US 6576764 B2 20030610
 US 2003120068 A1 20030626 US 2003-348757 20030123
 US 2003135043 A1 20030717 US 2003-368441 20030220
 PRIORITY APPLN. INFO.: US 1999-130047P P 19990419
 US 2000-182745P P 20000216
 US 2000-552485 A2 20000418
 US 2001-900646 A3 20010706
 US 2002-283093 A3 20021030

OTHER SOURCE(S): CASREACT 138:304301; MARPAT 138:304301
 GI



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IT 85650-52-8, Mirtazapine
 RL: IMP (Industrial manufacture); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)
 (preparation and crystallization of piperazine ring-containing
 compds. such as
 mirtazapine)
 RN 85650-52-8 CAPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-
 methyl- (9CI) (CA INDEX NAME)



AB Mirtazapine (I) was prepared by reacting substituted pyridine II [R1 = CH₂OH, CH₂Cl, CH₂Br, CH₂I; R2 = NH₂] with compound III [R3 = Cl, F, Br, I].

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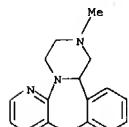
07/13/2004

L5 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

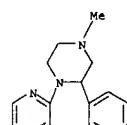
L5 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2002:406942 CAPLUS
 DOCUMENT NUMBER: 136:401782
 TITLE: Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
 INVENTOR(S): Maeda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi
 PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
 SOURCE: Eur. Pat. Appl., 10 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1209159	A2	20020529	EP 2001-111102	20010508
EP 1209159	A3	20030305		
R: AT, BE, CH, DE, DK, ES, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002065413	A1	20020530	US 2001-842871	20010427
AU 2001040301	A5	20020606	AU 2001-40301	20010430
JP 2002220390	A2	20020809	JP 2001-291863	20010925
PRIORITY APPLN. INFO.: JP 2000-359891 A 20001127				
OTHER SOURCE(S): CASREACT 136:401782				
AB Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual solvent, and which have an average particle diameter of from 10-50 μ m, are described where: one filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.				
IT 85650-52-8, Mirtazapine RL: IMP (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process); (process for the manufacture of anhydrous solvent-free mirtazapine crystals) RN 85650-52-8 CAPLUS CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)				

L5 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2001:880108 CAPLUS
 DOCUMENT NUMBER: 136:268247
 TITLE: Spectroscopic methods for determining enantiomeric purity and absolute configuration in chiral pharmaceutical molecules
 AUTHOR(S): Shah, Rekha D.; Nafie, Laurence A.
 CORPORATE SOURCE: The RW Johnson Pharmaceutical Research Institute, Spring House, PA, 19477-0776, USA
 SOURCE: Current Opinion in Drug Discovery & Development (2001), 4(6), 764-775
 CODEN: CODDFI; ISSN: 1367-6733
 PUBLISHER: PharmaPress Ltd.
 DOCUMENT TYPE: Journal, General Review
 LANGUAGE: English
 AB A review with refs. Anal. support, such as methods development, along with identification and characterization of intermediates and impurities, are critical in the development of a chemical process. The preparation of a drug substance requires the development of anal. methods for monitoring reactions and identifying impurities. Methods development for a chiral drug mol. is more difficult as the method must be capable of monitoring the overall reaction as well as possible racemization of starting materials and products. Chiral methods are often required to monitor the reaction steps of a synthesis, however, the development of enantiomeric purity methods are time-consuming and expensive. The use of chiroptical detectors, such as CD (CD), optical rotation (OR) and vibrational CD (VCD), can help to reduce or eliminate the need to develop chiral monitoring methods and also to predict absolute configuration. Recently, VCD has shown remarkable success with the latter and currently holds the most promise as a general, direct method that can be used as an alternative to X-ray crystallography. Each of the mentioned techniques can help anal. chemists to reduce the time associated with traditional enantiomeric purity methods development and to determine absolute configuration. This review will discuss the scope and limitations of these techniques for the rapid and routine determination of both enantiomeric excess and absolute configuration.
 IT 85650-52-8, Mirtazapine
 RL: AN7 (Analyte); ANST (Analytical study)
 (spectroscopic methods for determining enantiomeric purity and absolute configuration in chiral pharmaceuticals)
 RN 85650-52-8 CAPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



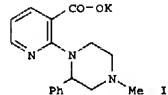
L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
 REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR
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L5 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2001435071 CAPLUS
 DOCUMENT NUMBER: 135:33494
 TITLE: Process for the preparation of a pyridinemethanol compound
 INVENTOR(S): Iishi, Eiichi; Yoshikawa, Kanami
 PATENT ASSIGNEE(S): Sunika Fine Chemicals Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 30 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042240	A1	20010614	WO 2000-JP6688	20000928
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
WO 2001042239	A1	20010614	WO 2000-JP5384	20000811
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AU 2000074472	A5	20010618	AU 2000-74472	20000928
EP 1238977	A1	20020911	EP 2000-962909	20000928
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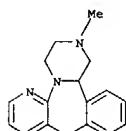
OTHER SOURCE(S): CASREACT 135:33494

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L5 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

AB A pyridinemethanol compound useful as an important intermediate for the preparation of mirtazapine effective as an antidepressant can be prepared by reducing a potassium salt of pyridinecarboxylic acid as represented by formula I with a metal hydride. Thus, 1-butanol 162, KCH 60.93, and 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-carbonitrile oxalate 40 g were heated to give potassium 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-carboxylate, which was reduced in THF with 12.5 g lithium aluminum hydride to give 21.75 g 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-methanol (yield 70.7%).
 IT 85650-52-8, Mirtazapine
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
 (preparation of pyridinemethanol compound as intermediate for mirtazapine)
 RN 85650-52-8 CAPLUS
 CN Pyrazino[2,1-*l*]pyrido[2,3-*c*][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

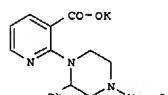


REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR
 THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
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L5 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2001435070 CAPLUS
 DOCUMENT NUMBER: 135:33493
 TITLE: Process for the preparation of a pyridinemethanol compound
 INVENTOR(S): Iishi, Eiichi; Yoshikawa, Kanami
 PATENT ASSIGNEE(S): Sunika Fine Chemicals Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 30 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042239	A1	20010614	WO 2000-JP5384	20000811
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WO 2001042240	A1	20010614	WO 2000-JP6688	20000928
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AU 2000064742	A5	20010618	AU 2000-74472	20000928
EP 1238977	A1	20020911	EP 2000-962909	20000928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AU	PRIORITY APPLN. INFO.: JP 1999-352514 A 19991213 WO 2000-JP5384 W 20000811 WO 2000-JP6688 W 20000928 US 6176688 B1 20020423 US 2000-706803 20001107 US 2002035255 A1 20020321 US 2001-98119 20011019 US 6437120 B2 20020820 US 2000-706803 A3 20001107			

OTHER SOURCE(S): CASREACT 135:33493
 GI



LS ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

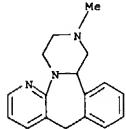
AB A pyridinemethanol compound serving as an important intermediate of mirtazapine useful as antidepressant can be prepared by reducing a potassium salt of a pyridinecarboxylic acid as represented by formula I with a metal hydride.

IT 85650-52-8P, Mirtazapine
RL: IMP (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of pyridinemethanol compound as intermediate for mirtazapine)

RN 85650-52-8 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LS ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:396868 CAPLUS
DOCUMENT NUMBER: 135:12412
TITLE: Anhydrous mirtazapine crystals and process for producing the same
INVENTOR(S): Iishi, Eiichi; Imamiya, Yoshiyuki
PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

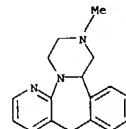
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001038329	A1	20010531	WO 2000-JP4835	20000719
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WO 2001038330	A1	20010531	WO 2000-JP6687	20000928
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AU 2000074471	A5	20010604	AU 2000-74471	20000928
AU 763502	B2	20030724	EP 2000-962908	20000928
EP 1225174	A1	20020724	EP 2000-962908	20000928
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
US 2002010372	A1	20020801	US 2002-41495	20020110
US 6552189	B2	20030422		
US 2003130504	A1	20030710	US 2003-337277	20030107
PRIORITY APPLN. INFO.:			JP 1999-333049 A 19991124	
			JP 2000-67476 A 20000310	
			WO 2000-JP4835 W 20000719	
			WO 2000-JP6687 W 20000928	
			US 2000-697329 A3 20001027	
			US 2002-41495 A3 20020110	

AB This document discloses : lowly-hygroscopic anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h; a process for producing anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C at a relative humidity of 75% under atmospheric pressure for 500 h characterized by drying crystals of mirtazapine hydrate; and a process for producing crystals of mirtazapine hydrate characterized by crystallizing crude mirtazapine by using a water soluble polar organic solvent and water. By using this production method, stable anhydrous mirtazapine having little hygroscopicity can be produced by a convenient industrial method. The anhydrous mirtazapine

LS ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
crystals are usable as active ingredients in an antidepressant.
IT 341512-89-8 341512-90-1
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(preparation of anhydrous mirtazapine crystals)

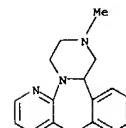
RN 341512-89-8 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,4a,9-hexahydro-3-methyl-, hydrate (2:1) (9CI) (CA INDEX NAME)



●1/2 H₂O

RN 341512-90-1 CAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,4a,9-hexahydro-3-methyl-, hydrate (9CI) (CA INDEX NAME)



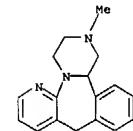
●x H₂O

IT 85650-52-8P, Mirtazapine
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of anhydrous mirtazapine crystals)

RN 85650-52-8 CAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

LS ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



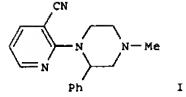
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

LS ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2001:265372 CAPLUS
 DOCUMENT NUMBER: 134:280862
 TITLE: Process for the preparation of a piperazine derivative
 INVENTOR(S): Maeda, Chiharu; Iishi, Eiichi; Wang, Weigui; Imamiya, Yoshiyuki
 PATENT ASSIGNEE(S): Sumika Fine Chemicals Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 31 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001025185	A1	20010412	WO 2000-JP5432	20000814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
WO 2001023345	A1	20010405	WO 2000-JP6650	20000927
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1136470	A1	20010926	EP 2000-962874	20000927
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US 6495685 B1 20021237 US 2000-697140 20001027	JP 1999-280378 A 19990930			
PRIORITY APPLN. INFO.:	WO 2000-JP5432 W 20000814			
	WO 2000-JP6650 W 20000927			

OTHER SOURCE(S): CASREACT 134:280862
 GI

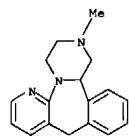
LS ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



AB A process for the preparation of a piperazine derivative, namely 2-(4-methyl-3-phenylpiperazin-1-yl)-3-cyanopyridine (I), comprises reacting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyanopyridine in the presence of a base and an alkali metal halide in an aprotic polar organic solvent. This piperazine derivative I and its oxalate are useful as intermediates for the preparation of mirtazapine. Thus, 11.4 kg N-methylethanolamine was added dropwise to a solution of 20 kg styrene oxide in 38 kg DMF at .apprx.80°, stirred at .apprx.80° for 3 h, and cooled to room temperature to give a DMF solution of N-(2-hydroxyethyl)-N-methyl-2-hydroxy-2-phenylethylamine which was added dropwise to a solution of 45 kg SOC12 in 67.4 kg toluene at 0-25°, stirred at 45-55° for 2 h, cooled at 25°, treated with 95 kg H2O and then with 30 weight% aqueous KOH at 0-25°, and left to stand for phase separation. The organic and aqueous phase were separated and the aqueous phase was extracted with 55 kg toluene, followed by combining the extract and the organic phase, drying over 4.8 kg MgSO4, treating with 4.8 kg activated clay and filtration, and washing with 19.9 kg PhMe to give a toluene solution of N-(2-chloroethyl)-N-methyl-2-chloro-2-phenylethylamine (II). To the toluene solution was introduced 5.5 kg HCl(g) at 10-35° and stirred at 20-25° for 2 h and the precipitated crystals were filtered and washed with 69 kg toluene to give 30 kg II.HCl. EtOAc (100 mL), 460 mg Bu4NBr, and 20.1 g II.HCl were added to 132 g 28% aqueous NH3 at room temperature and stirred at 40-45° for 3 h, followed by separating the organic layer and extracting the aqueous layer with EtOAc (2 + 30 mL) and the combined organic layer evaporated in vacuo to give 53.8% 1-methyl-3-phenylpiperazine (III) (7.1 g). III 5.51, 2-chloro-3-cyanopyridine 4.47, Et3N 4.1, and KI 5.20 g were added to 11 mL DMF and stirred at 125-130° for 24 h, followed by removing Et3N and DMF under reduced pressure, adding 20 mL H2O and 25 mL EtOAc to the residue, adjusting pH at 8-9 with 10% NaOH, separating the organic phase, and extracting the aqueous layer with EtOAc (3 + 30 mL), washing the combined organic layer with 5% NaHCO3, drying and concentration, and crystallization from

LS ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

IT 85650-52-8, Mirtazapine
 RU: PNU (Preparation, unclassified); PREP (Preparation)
 (preparation of (methylphenylpiperazinyl)cyanopyridine as intermediate for mirtazapine)
 RN 85650-52-8 CAPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



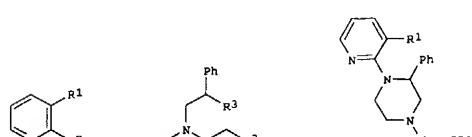
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

LS ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
 ACCESSION NUMBER: 2000:756528 CAPLUS
 DOCUMENT NUMBER: 133:321900
 TITLE: Novel synthesis and crystallisation of piperazine ring-containing compounds such as mirtazapine
 INVENTOR(S): Singer, Claude; Liberman, Anita; Finkelstein, Nina
 PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
 SOURCE: PCT Int. Appl., 22 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000062782	A1	20001026	WO 2000-US10357	20000418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1178805	A1	20020213	EP 2000-923457	20000418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO	HR 2001000747 A1 20021231 HR 2001-747 20011015			
US 2003088094 A1 20030508 US 2002-283093 20021030	US 6576764 B2 20030610 US 2003120068 A1 20030626 US 2003-34757 20030123			
PRIORITY APPLN. INFO.:	US 6576764 B2 20030610 US 2003120068 A1 20030626 US 1999-130047P P 19990419 US 2000-552445P A3 20000418 WO 2000-US10357 W 20000418 US 2001-500646 A3 20010706 US 2002-283093 A3 20021030			

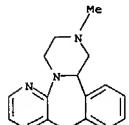
OTHER SOURCE(S): CASREACT 133:321900; MARPAT 133:321900
 GI



AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I (R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2) with

07/13/2004

LS ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
 II (R3 = Cl, F, Br, I) followed by treating the resulting piperazine III
 with H2SO4. The mirtazapine intermediate
 1-(3-carboxypyridyl-2)-4-methyl-
 1-phenylpiperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-
 methyl-2-phenylpiperazine with KOH at a temp. of at least about
 130°C. The present invention also relates to new processes for
 recrystn. of mirtazapine from crude mirtazapine.
 IT 85650-52-8; Mirtazapine
 RL: BAE (Biological activity or effector, except adverse); BSU
 (Biological study, unclassified); IMP (Industrial manufacture); PUR (Purification or
 recovery); SPA (Synthetic preparation); THU (Therapeutic use); BIOL
 (Biological study); PREP (Preparation); USES (Uses)
 (novel synthesis and crystallisation of piperazine ring-containing
 compds. such as mirtazapine)
 RN 85650-52-8 CAPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-
 methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT